REMARKS

A restriction requirement was issued in the above named case on February 13, 2003. At that time, the Applicants elected the claims directed to the use of phospholamban peptides for the treatment of heart failure. At this time, the Applicants elect to pursue the second invention of the application, the use of nucleic acid expression constructs for the treatment of heart failure. The Applicants present the above claims for examination and the following comments for consideration at this time.

The Applicants have claimed delivery of an expression construct comprising a coding sequence and a promoter functional in heart. The Applicants submit that as of the date of the filing of the priority application in the case, November 2, 1998, a number of methods, constructs and apparatuses for delivery of such gene therapy agents was well known to those skilled in the art. In US Patent 5,797,870 (March et al.), issued August 25, 1998, the following series of gene therapy agents are listed in column 5, lines 2-18:

> Agents comprise naked DNA or DNA compositions for delivery of genetic information in vivo or cells which have been genetically modified in vitro. Methods for transfer of genetic information generally fall into one of three categories. First, DNA may be delivered by physical means, including microinjection, electroporation, biobalistic or particle bombardment, jet injection, and others. Second, DNA may be delivered by chemical means, using calcium phosphate, DEAE dextran, polylysine conjugates, "starburst" dendrimer conjugates, polybrene-dimethyl sulfoxide, receptor-mediated uptake systems such as asialoglycoprotein and transferrin, liposomes, virion like particles (VLP's), intra-cellular targeting ligands and others. Third, DNA may be delivered by biological means, including retroviral vectors such as Moloney murine leukemia virus (MoMLV), adenovirus vectors and adeno-associated virus vectors (AAV), herpes simplex virus vectors, semliki forest virus vectors, sindbis virus vectors and others.

Apparatuses and viral constructs for delivery of gene therapy agents to the heart were also known. The Applicants have enclosed a few representative patents (Igo, US Patents 5,634,895 and 5,827,216 issued June 3, 1997 and October 28, 1998 respectively; and Grabek, US Patent 5,931,810 issued August 3, 1999) to demonstrate methods and apparatuses for delivery of material to the heart at the time of the application.

Representative references have also been enclosed describing gene therapy agents and their methods of delivery that were known at the time of the filing of the priority document of the instant application. Hammond et al. teach the use of adenoviral vectors for delivery of genes to the heart (US Patent 6,100,242, issued August 8, 2002, published as a PCT application September 6, 1996, see claim 1). Methods to improve the efficiency of gene transfer to rabbit hearts is taught by Donohue et al. (*Proc. Natl. Acad. Sci. USA;* **94**:4664-8, 1997, last sentence of abstract). Rebolledo et al teach that and HIV-1 derived vector can be used for delivery of genes to human fetal cardiac myocytes (*Circ Res;* **83**:738-42, 1998 last sentence of abstract). No *in vivo* data are presented as HIV does not infect non-human cells. Dazu et al. teach the delivery of nucleic acids to a variety of tissues *in vivo* (see Table 1) including rat heart using a fusogenic viral liposome based on the hemagglutinating virus of Japan (HVJ)-liposome complex (*Proc. Natl. Acad. Sci. USA;* **93**:11421-5, 1996). Hajjar et al. demonstrate delivery of phospholamban to rat heart with sufficiently high efficiency to result in modulation of ventricular function (*Proc. Natl. Acad. Sci. USA;* **95**:5251-5256, 1998). The Applicants submit that at the time of the filing of the priority document of the instant invention, the field of gene delivery was established and methods for gene delivery to the heart were well known to those skilled in the art.

FEES

It is believed that there are no fees due with this preliminary amendment other than the filing fee for the application. If an additional fee is due, the Commissioner is hereby authorized to charge any additional fees to Deposit Account 02-4070 referencing case number 6627-P9025C.

CONCLUSIONS

The Examiner is respectfully requested to enter the amendment and comments into the case prior to examination. If the Examiner has any questions regarding the case that may be resolved by a telephone conference, the Examiner is encouraged to call the Agent for Applicant, collect, at the number listed below.

Respectfully submitted,

Dated: November 10, 2003

By: _____

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